Remarks

I. Status of the Claims

Claims 1-13 are under examination on their merits. Claims 14-17 were previously withdrawn.

II. Examiner Interview

Applicant thanks the Examiner for the courtesy extended during the telephonic interview conducted on November 15, 2010 with the undersigned representative Elaine Chang. During the interview, Applicant sought clarification with regard to the rejection under 35 U.S.C. § 102(e). No agreement was reached.

III. Claim Rejections under 35 U.S.C. §102

The Office has maintained the rejection of claims 1-13 under 35 U.S.C. §102(e) as being anticipated by Barone *et al.* (WO 2004/105751, hereinafter "Barone"). Specifically, the Office asserts that Barone teaches a method of treating hypertension in a mammal comprising administering an effective amount of PDE4 inhibitor. The Office further asserts that the subject undergoing the method of Barone implicitly encompasses patients suffering from all types of hypertension including salt-sensitive hypertension.

Applicant respectfully traverses the rejection based on the following argument. In addition, Applicant herewith submits a Declaration by the inventor Dr. Robert Danziger pursuant to 37 C.F.R. § 1.132 (hereinafter "the Declaration"), and requests that the Office fully consider all rebuttal evidence set forth in this response and in the Declaration. *See In re Sullivan*, 84 USPQ2d 1034, 1038 (Fed. Cir. 2007) (holding that the Office must consider rebuttal evidence put forth in a declaration by a patent applicant).

The Applicant respectfully submits that Barone does not anticipate the instant claims for at least the following reasons: (1) it does not identically disclose every element of the claimed invention as required under 35 U.S.C. §102; and (2) it does not enable the claimed invention, as determined by the following methodical analysis of the factors set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

1. Barone does not identically disclose the claimed invention

The Federal Circuit mandates that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumitomo Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989) (emphasis added). The exclusion of a claimed element from a reference, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.,* 220 U.S.P.Q 193, 198 (Fed. Cir. 1983).

Claim 1 of the instant application recites:

> A method of treating salt-sensitive hypertension in a mammal suffering therefrom, said method comprising the step of administering a therapeutically effective amount of a cyclic nucleotide phosphodiesterase (PDE) inhibitor to said mammal.

The Office asserts on p. 3 of the pending Final Action, "Barone *et al.* teaches a method of treating hypertension in a mammal, comprising administering an effective amount of PDE4 inhibitor such as rolipram." While acknowledging that Barone does not teach salt-sensitive hypertension, the Office nevertheless asserts that Barone's purported hypertension patient population implicitly encompasses patients suffering from salt-sensitive hypertension. The Office reasons that this is so because "the patient population of the instant invention [subjects with salt-sensitive hypertension] substantially overlaps with that of the reference [purported subjects suffering from hypertension in general]." See p. 3 of the Final Action (citing Weinberger *et al.*, the Office asserted that among all hypertensive patients, 51% are classified as salt-sensitive hypertension). Thus, the Office continues, Barone's purported teaching of treating hypertension with a PDE inhibitor reads on the instant claims even though the claims are directed specifically to *salt-sensitive* hypertension.

Applicant respectfully disagrees. As stated by Dr. Danziger in the Declaration, salt-sensitive hypertension is a unique subset of hypertension having distinct physiology, etiology and pharmacology as compared with non-salt-sensitive hypertension. See paragraph 6 of the Declaration. For example, it has been shown that angiotensin receptor blockade ameliorated renal injury in animals with salt-resistant, but not salt-sensitive, hypertension. See paragraph 7 of the Declaration. Further, Bayorh *et al.* showed that dietary salt reduces plasma levels of prostacyclin, a vasodilator, in subjects with salt-resistant hypertension, but not salt-sensitive

hypertension. *Id.* In addition, Unlap *et al.* showed that the Na/Ca exchanger in salt-sensitive rats and salt-resistant rats differ in amino acid sequences as well as functions. *Id.*

Further, salt-sensitive hypertension is a unique subset of hypertension, which responds differently to PDE inhibitors as opposed to non salt-sensitive hypertension. This is evident at least from Example 1 and Figures 1A-1B of the instant specification, which demonstrate substantial differences in the response kinetics to the PDE4 inhibitor rolipram in the salt-sensitive Dahl SS/jr rats and salt-resistant, spontaneously hypertensive rats (SHR).

As stated at paragraph [0065] of the published application US 2009/0042951, salt-sensitive hypertensive rats exhibited a very significant and prolonged drop in blood pressure in response to rolipram injection (Figure 1A). On the other hand, injection of rolipram did not result in a significant drop in blood pressure in salt-resistant hypertensive rats (Figure 1B). The differences in the response kinetics to rolipram injection confirm that salt-sensitive hypertension and salt-resistant hypertension are different disorders. See [0065]. Thus, the term "hypertension" as broadly disclosed by Barone fails to appreciate the differences between salt-sensitive hypertension from other types of hypertension with respect to the response to PDE inhibitors.

This is important because the purported all-encompassing "hypertensive population" of Barone would inevitably include hypertensive patients that do *not* respond to the PDE inhibitors. The claimed method, however, is directed specifically to salt-sensitive hypertensive patients, patient population first found to be responsive to PDE inhibitors by Dr. Danziger. Thus, the Office's assertion that "Barone *et al.* teaches the administration of the same PDE inhibitor (rolipram) for the *same patient population* (i.e., mammal suffering from hypertension) *as the instant invention*" is incorrect. See p. 4 of the Final Action (emphasis added). Barone does not recognize that only salt-sensitive hypertensive subjects respond to the PDE inhibitors; therefore, Barone does not teach treating specifically salt-sensitive hypertension using the PDE inhibitors. Indeed, Barone never demonstrated measuring blood pressure and its reference to hypertension is merely based on speculation.

In fact, as argued in Applicant's response dated March 11, 2010, the skilled artisan would have understood that Barone does not teach treating hypertension at all. Barone only discloses methods of reducing cardiovascular pathology in a mammal, which is explicitly referred to as "cardiac hypertrophy, coronary heart disease, arrhythmia, restricted coronary blood flow, arteriosclerosis, heart failure, congestive heart failure (CHF), and myocardial infarction."

Nowhere does Barone list hypertension, let alone salt-sensitive hypertension, as a cardiovascular pathology to be treated by the method disclosed therein.

The Office further asserts that claim 5 of Barone discloses the instant invention. The Applicant disagrees. Claim 5 reads, "The method of claim 1, wherein the mammal [is] suffering from hypertension." Applicant respectfully submits that "hypertension" as recited in claim 5 is not claimed as a subset or limitation to the "cardiovascular pathology" being treated in claim 1, from which claim 5 depends. Claim 5 specifies only that the mammal being treated suffers from hypertension, but does not build on the antecedent recitation of "cardiovascular pathology" in claim 1 (in direct contrast, claims 2-4 of Barone specifically recite "wherein the cardiovascular pathology is cardiac hypertrophy," "wherein the cardiovascular pathology is heart failure," and "wherein the cardiovascular pathology is congestive heart failure," respectively). Thus, the language in claim 5 does not specify treatment of hypertension, but rather that the subject patient *also suffers* from hypertension. A reference must be interpreted both for what it teaches and what it does not, and particularly in view of the highly specific and technical structure of patent claims and the importance of word choice therein, the use by Barone of different words in claim 5 compared to claims 2-4, one of skill in the art would have understood that Barone was not claiming methods of treating hypertension, but rather the subset of patients suffering from cardiovascular pathology *who also suffer from hypertension*. This is further supported by the complete absence of experimentation in Barone, prophetic or actual, designed to measure blood pressure in the hypertrophic mice; if the Barone reference indeed showed treatment of hypertension using PDE inhibitors, it would perforce contain disclosure of blood pressure in such mice, and particularly changes in blood pressure upon administration of PDE inhibitors. It does not. Applicant submits that the Office has mischaracterized the teachings of Barone by unsubstantiated extrapolation of the language in claims 2-4 to claim 5.

Even the aortic banded, hypertrophic mice do not represent the "same patient population" as the instant invention. As stated by Dr. Danziger in paragraph 10 of the Declaration provided herewith, "the aortic banded mice used by Barone may be a model of cardiac hypertrophy; but it is not a model of salt-sensitive hypertension." In fact, arterial hypertension that has been reported with aortic banding occurs on a regular diet, not high-salt diet. See paragraph 9 of the Declaration. Thus, Applicant respectfully contends that the evidence of record does not support

the Office's assertion that Barone teaches treatment of the "same patient population" as the instant invention.

Because Barone does not identically disclose any treatment whatsoever for hypertension, more specifically *salt-sensitive* hypertension that is the subject of the instant application, Applicant submits that Barone does not anticipate the claimed methods of treating salt-sensitive hypertension using a cyclic nucleotide PDE inhibitor.

2. Barone does not enable any method of treating or reducing salt-sensitive hypertension

Regardless of the question of whether Barone teaches every element of the claimed invention (which Applicant respectfully contends that it does not), a patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005). The prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation. *Id. See also Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research*, 68 U.S.P.Q. 2d 1373, 1376 (Fed. Cir. 2003).

Simply put, it is insufficient for a purportedly anticipating reference to simply name or describe the desired subject matter, if it cannot be produced without undue experimentation. *Elan Pharmaceuticals*, 68 U.S.P.Q. 2d at 1376. These principles are even more compelling where, as here, the cited Barone reference failed even to name or describe the claimed method of treating *salt-sensitive* hypertension using a PDE inhibitor. These rubrics for patent examination are important with regard to the declaration presented with Applicant's March 11, 2010 response, which the Office dismissed as being "irrelevant. (The Office asserted that "the declaration stating that a drug that is purportedly effective in treating hypertrophy does not necessarily reduce hypertension is ***irrelevant*** since Barone explicitly teaches a method of treating hypertension comprising administering a PDE inhibitor such as rolipram with sufficient disclosure for enablement." See p. 5 of the Final Action, emphasis added.) On the contrary, as set forth above Barone does not in fact teach (expressly or impliedly) the invention claimed by Applicant in his application. Applicant also reminds the Office that it must fully consider all rebuttal evidence set forth both in this response and in the attached Declaration. *See in re*

Sullivan, 84 USPQ2d 1034, 1038 (Fed. Cir. 2007) (holding that the Office must consider rebuttal evidence put forth in a declaration by a patent applicant).

With regard to undue experimentation, the court in *Elan Pharmaceuticals* referred to the factors delineated in *In re Wands* in determining enablement of a prior art. *Id.* (citing *In re Wands*, 858 F.2d 731, 737). The factors to be considered when determining whether a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, "(A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure." *In re Wands*, 858 F.2d at 737. These factors are analyzed below with respect to the teachings of Barone and the instant claims.

(A) The breadth of the claims

The instant claims are drawn to methods of treating specifically salt-sensitive hypertension in a mammal comprising administering a cyclic nucleotide PDE inhibitor to the mammal. The Office asserts that the breadth of the Barone disclosure is the entirety of hypertension, regardless of etiology or pathology. Barone, however, fails to appreciate the differences between salt-sensitive hypertension and other types of hypertension with respect to the response to the PDE inhibitors.

(B) The nature of the invention

Applicant identified cyclic nucleotide PDE inhibitors as effective therapeutics for reducing blood pressure specifically in subjects with salt-sensitive hypertension. The finding was demonstrated by comparative experimental evidence obtained from actual experiments performed in Dahl salt-sensitive rats (a well-accepted experimental animal model for human salt-sensitive hypertension) and spontaneously hypertensive rats (a model for non salt-sensitive hypertension).

Barone provides no experimental data for the treatment of hypertension, let alone salt-sensitive hypertension. Actual experimental data is necessary especially in this case because salt-sensitive hypertension and non salt-sensitive hypertension are conditions having distinct

physiology, etiology and pharmacology. For example, as stated in the Declaration, Dr. Danziger pointed out that angiotensin receptor blockade ameliorated renal injury in animals with salt-resistant, but not salt-sensitive, hypertension. See paragraph 7 of the Declaration. Further, dietary salt reduces plasma levels of prostacyclin, a vasodilator, in subjects with salt-resistant hypertension, but not salt-sensitive hypertension. See paragraph 7 of the Declaration. In addition, Na/Ca exchanger in salt-sensitive rats and salt-resistant rats differ in amino acid sequences as well as functions. *Id*. Given the differential response of salt-sensitive hypertension as opposed to non salt-sensitive hypertension, a purported anticipatory art must (at a minimum) recognize the difference and demonstrate the therapeutic effect by actual experimentation. Barone provides neither.

Barone's teachings are limited to reduction of left ventricular mass of aortic-banded hypertrophic mice treated with rolipram. The aortic-banded mice in Barone are not recognized in the art as a model for salt-sensitive hypertension. See paragraph 10 of the Declaration. This is in part because arterial hypertension that has been reported with aortic banding occurs on a regular diet, not high-salt diet. See paragraph 9 of the Declaration. Thus, the disclosure in the Barone reference does not enable one of ordinary skill in the art to practice the claimed invention of treating salt-sensitive hypertension.

(C) The state of the prior art

Prior to the instant application, the use of cyclic nucleotide PDE inhibitors to treat *salt-sensitive* hypertension was not known, and Barone's disclosure did not fill that void. Barone does not recognize the selective effects of PDE inhibitors on salt-sensitive hypertension. Because the state of the prior art teaches that the aortic banded rats developed hypertension under regular diet, not high salt diet, one of skill in the art would have understood that Barone's aortic-banded mice did not suffer from *salt-sensitive* hypertension. Therefore, the skilled artisan would not have assumed that the use of PDE inhibitors in these mice would constitute any treatment of salt-sensitive hypertension.

Thus, the state of the prior art would not have led one skilled in the art to arrive at the claimed invention from the teachings of Barone.

(D) The level of one of ordinary skill

Even if the level of ordinary skill in the art is high, the ordinarily skilled worker would not have had any basis for challenging the state of the art based on the Barone teachings, and would not have had any reason to assume that Barone's broad, indiscriminative teaching of hypertension or specific teaching with respect to aortic-banded mice enabled any treatment of *salt-sensitive* hypertension.

(E) The level of predictability in the art

Dr. Danziger's Declaration and the art cited therein demonstrate that the level of predictability in the art is low. Barone's teaching certainly does not contribute to or enhance the predictability in the art. First of all, Barone does not recognize the selective responsiveness of salt-sensitive hypertension. Secondly, it was known in the art that a drug that reduces hypertrophy does not always reduce blood pressure and thus does not necessarily reduce hypertension.

That is partly because the Barone reference is limited as a model for cardiac hypertrophy, and cardiac hypertrophy is a disease of many etiologies. As pointed out by Dr. Danziger, although hypertension may cause pressure overload, which may in turn lead to cardiac hypertrophy, cardiac hypertrophy can arise from etiologies completely unrelated to blood pressure buildup. See paragraph 13 of the Declaration. For example, hypertrophic cardiomyopathy is an inherited cardiac muscle disorder manifested by the thickening of heart muscle that is not caused by hypertension; in another example, amyloidosis in the heart can lead to cardiac hypertrophy but has no relation to hypertension. *Id*. Thus, a drug that reduces hypertrophy does not always reduce blood pressure and thus does not necessarily reduce hypertension. See paragraph 14 of the Declaration.

Even in hypertension-induced hypertrophy, a drug that alleviates hypertrophy does not necessarily reduce the underlying cause of hypertension. Dr. Danziger in paragraph 15 of the Declaration provided several such examples. Ito *et al*. showed in 1993 that the endothelin receptor antagonist BQ123 reduced cardiac hypertrophy provoked by left ventricular overload in rats. The drug, however, exhibited no effects on aortic pressure in the animals. *See* paragraph 15 of the Declaration. Similarly, Date *et al*. demonstrated that the antioxidant N-2-Mercaptopropionyl glycine (MPG) attenuated pressure overload-induced cardiac hypertrophy in

mice; however, MPG was ineffective in reducing high blood pressure -- the underlying cause of hypertrophy in the animals. *Id.*

In addition, it was also known at the time of filing that effective therapy for hypertrophy does not always reduce blood pressure in an animal that experiences hypertrophy and also suffers from hypertension. See paragraph 16 of the Declaration. Dr. Danziger cited the Nakagami reference in which a mouse model was used that exhibited angiotensin II-induced hypertrophy and angiotensin II-induced hypertension. See paragraph 17 of the Declaration. The reference showed that the antioxidant, N-acetylcysteine (NAC), was effective in attenuating angiotensin II-induced cardiac hypertrophy. However, angiotensin II-induced increase in blood pressure was not affected by the treatment of NAC. *Id.*

Therefore, a person experienced in the field of cardiovascular pathology would have appreciated the unpredictability and would not have applied treatments for hypertrophy, such as Barone's, to the treatment of hypertension, let alone salt-sensitive hypertension, with a reasonable expectation of success.

(F) The amount of direction provided

MPEP § 2164.03 states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." Because the level of predictability in the art is low, the amount of direction required to arrive at the instant invention is high. Thus, without the direction provided by the Applicant, one of skill would have been unable to start with Barone and arrive at the claimed invention without significant experimentation. And the evidence set forth herein establishes without question that the Barone reference contains *no* direction regarding treating hypertension using PDE inhibitors; the reference does not even measure blood pressure in the experimental mice disclosed therein.

(G) The existence of working examples

Barone does not provide any working examples for methods of treating hypertension, let alone salt-sensitive hypertension, using any cyclic nucleotide PDE inhibitors. Barone's examples of testing the effects of rolipram in aortic banded mice are irrelevant to the enablement

of the instant claims, because the aortic banded mice of Barone's is not a model for salt-sensitive hypertension. See paragraph 10 of the Declaration.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

A substantial quantity of experimentation would have been required to arrive at the claimed invention from Barone, which broadly discloses "hypertension" and does not recognize that only salt-sensitive hypertension is responsive to PDE inhibitors. It was the Applicant, not Barone, that demonstrated the specific effectiveness of PDE inhibitors on salt-sensitive hypertension (and not hypertension generally). After all, the Office estimates that nearly 50% of the hypertension is *not* salt-sensitive hypertension. The Office further asserts that "[t]he subject undergoing the method of the reference [Barone] implicitly encompasses patients suffering from all types of hypertension." Thus, nearly 50% of the subjects purportedly taught by Barone are likely to be non-responsive to the treatment of the claimed invention. Barone's broad, indiscriminative disclosure does not teach or suggest how to identify a responsive patient population. Accordingly, Barone does not enable the claimed invention because undue experimentation would be required.

In summary, the nature of the invention and state of the prior art, especially the differential effects of a PDE inhibitor on salt-sensitive vs. salt-resistant hypertension, required actual demonstration of responsiveness to the PDE inhibitors to be enabling; Barone is devoid of any such teachings. The level of predictability in the art was low and requires significant direction; Barone is devoid of any such teachings. Moreover, Barone disclosed no working examples directed toward treatment of salt-sensitive hypertension. The principles underlying application of the criteria of enablement to the content of the prior art were discussed in *In re Donahue*, in which the Federal Circuit stated:

> It is well settled that prior art under 35 U.S.C. 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that

disclosure will not suffice as prior art if it is not enabling. *In re Donahue*, 766 F.2d 531, 533 (Fed. Cir. 1985). (Emphasis added.)

Based on the above analysis Applicant respectfully contends that one skilled in the art could not have combined the teachings of Barone with her own knowledge to arrive at the claimed invention. Thus, Barone has not sufficiently described the claimed invention to have placed the public in possession of it. Accordingly, Barone is not anticipating prior art because it is not enabling.

In view of Barone's failure both to identically disclose the claimed invention and to enable the claimed invention, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) based on Barone.

IV. Conclusion

The Applicant believes that all conditions for allowance have been met, and a favorable decision is earnestly solicited. If it would be helpful, the Examiner is invited to contact the undersigned representative at 312-913-0001.

Respectfully submitted,

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